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Note

One pot stereoselective synthesis of isoxazolines from N-phenyl-α- chloro nitrone

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Isoxazolines have been synthesized from N-phenyl-α-chloro nitrone using 1,3 dipolar cycloaddition reaction with alkynes and the reactions are found to be highly stereoselective in nature. The products have been characterized by analytical and spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) data.

Keywords: N-phenyl-α-chloro nitrone, 1,3 DCR, isoxazolines, stereoselectivity

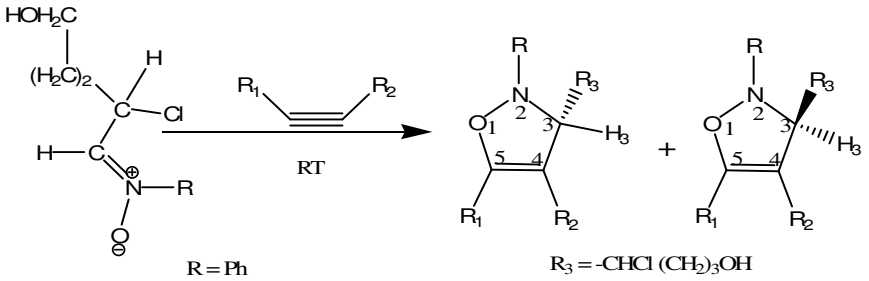
In continuation of our earlier work on isoxazolidine synthesis using α-chloro and α amino nitrones in solid phase and in hydrated media[1-3], we now wish to report an efficient method for the stereoselective synthesis of isoxazolines from N-phenyl-α-chloro nitrone with an excellent yield (**Table I**). 1,3 Dipolar cycloadditions are powerful methods for constructing a variety of five-membered heterocycles in a convergent manner from relatively simple precursors and these heterocycles have a variety of applications including as antibacterial agents[4]. Cycloadditions of alkynes even with electron deficient and unsymmetrical alkynes are often conducted at elevated temperature[5]. In this communication we have reported synthesis of isoxazolines at room temperature with high yield. This is due to the fact that N-phenyl-α-chloro nitrone has considerably higher ionization potential than normal nitrones due to the electron withdrawing effect of chlorine and therefore nitrone (LUMO) - dipolarophile (HOMO) interactions are so important that cycloadditions take place at room temperature[6].

Results and Discussion

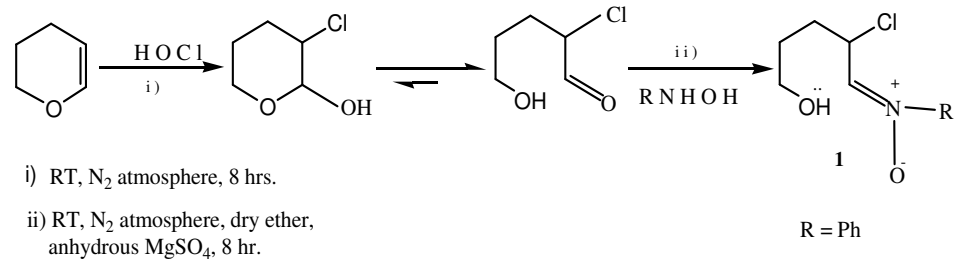
In an initial investigation, we examined the reaction of nitrone **1** with ethyl propiolate at elevated temperature having 34% yield of isoxazoline in 12 hr while at room temperature 92% yield of isoxazolines are reported in 12 hr which indicates the decomposition of the nitrone at elevated temperature. This could also be explained due to secondary orbital effect between the carbon of the nitrone (HOMO) and the adjacent atom of the electron withdrawing group of the dipolarophile (LUMO)[7]. The concerted nature of these cycloaddition reactions with nitrone as 1,3 dipole has been generally accepted. The region-selectivity in these reactions was rationalized by using the frontier orbital theory[8]. The ethyl propiolate adduct corresponds to this theory. Therefore, the 5 substituted adduct for ethyl propiolate is due to LUMO (nitrone)- HOMO (dipolarophile) interaction. For the present study, we have chosen highly electron deficient and unsymmetrical alkynes like dimethyl acetylene dicarboxylate, phenyl methyl propiolate and ethyl propiolate respectively to study the stereo-selectivity in these cycloadditions.

Excellent diastereofacial selectivity is observed in nitrone additions described here with alkynes. The addition of N-phenyl-α-chloro nitrone **1** (**Scheme I,** R = Ph) to alkyne results in a mixture of diastereoisomer **2a-4a** and **2b-4b** (**Scheme II,** almost 70 : 30 ratio in all cases). These results can be rationalized by an exo approach of the nitrone for the major cycloadducts (**2a-4a**) which have the Z configuration (transition state **I**)[9]. The minor cycloadducts (**2b-4b**) are formed by the endo approach of Z nitrone (transition state **II**)[10]. However these results can also be explained by an endo approach of the nitrone in an E configuration (transition state **III**) for the major adduct and the exo approach of this isomer for the minor adduct (transition state **IV**)[10]. Most relevant are the coupling constants ($J_{H3,CHCl}$; $J_{H3,\ H4}$ for **4**) of the diastereo-isomers. For **2a-4a** (R = Ph), this coupling constant is almost 9.2 to 9.3 Hz, implying a *cis* relationship between H_3 and CHCl and also H_3 and H_4 (for **4a** only) whereas **2b-4b** (R = Ph) has a coupling constant of 2.5 to 2.58 Hz which implies a *trans* relationship between H_3 and CHCl and also H_3 and H_4 (for **4b** only)[11-14]. Comparing the ^{1}H NMR spectrum of **2a-4a** and **2b-4b**, we suggest the major and minor conformers of isoxazoline ring systems[11] for **2a-4a** and **2b-4b** (**Figure 1**). All the cycloadducts are stable and detailed study of the mass spectrum (**Scheme III**) reveals that prominent molecular ion peak and base peaks are obtained as expected. Like other isoxazoline

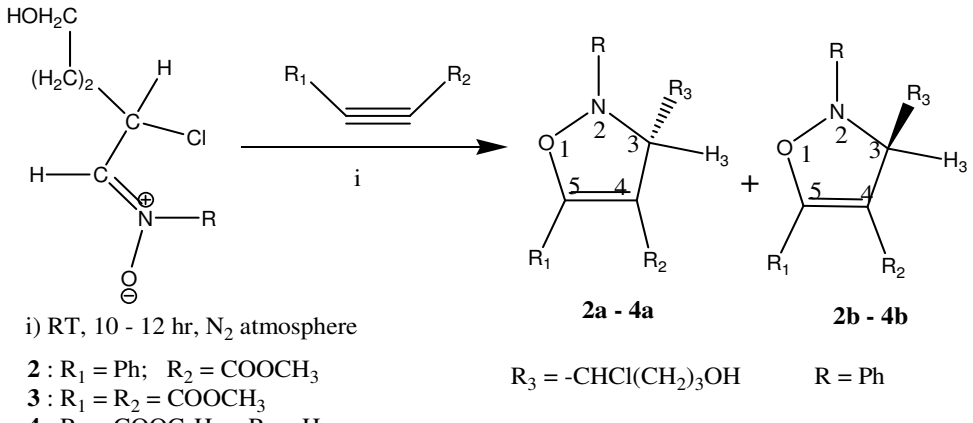
Table I



Entry	Nitrone	Dipolarophile	Time (hr)	Cycloadducts (diastereoisomers)	Total Yield (%)
1	N-phenyl-α-chloro nitrone	Phenyl methyl propiolate	10	Pale yellow gummy liquids	96
2	N-phenyl-α-chloro nitrone	Dimethyl acetylene dicarboxylate	10	Red & dark red liquids	92
3	N-phenyl-α-chloro nitrone	Ethyl propiolate	12	White viscous liquids	92



Scheme I



Scheme II

derivatives reported in the literature[5,7,10], we have also obtained expected fragmentation peaks due to the development of different aziridine derivatives. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, $COOCH_3$ for dimethyl acetylene dicarboxylate and $COOC_2H_5$ for ethyl propiolate respectively. Hence it is confirmed that during mass fragmentation, the adducts underwent rearrangement to aziridine derivatives. The detail mass fragmentation pattern is shown in **Scheme III**. In conclusion, the present procedure provides an efficient methodology for the synthesis of isoxazoline and their derivatives with high stereoselectivity. The notable advantages offered by this method are simple operation, mild

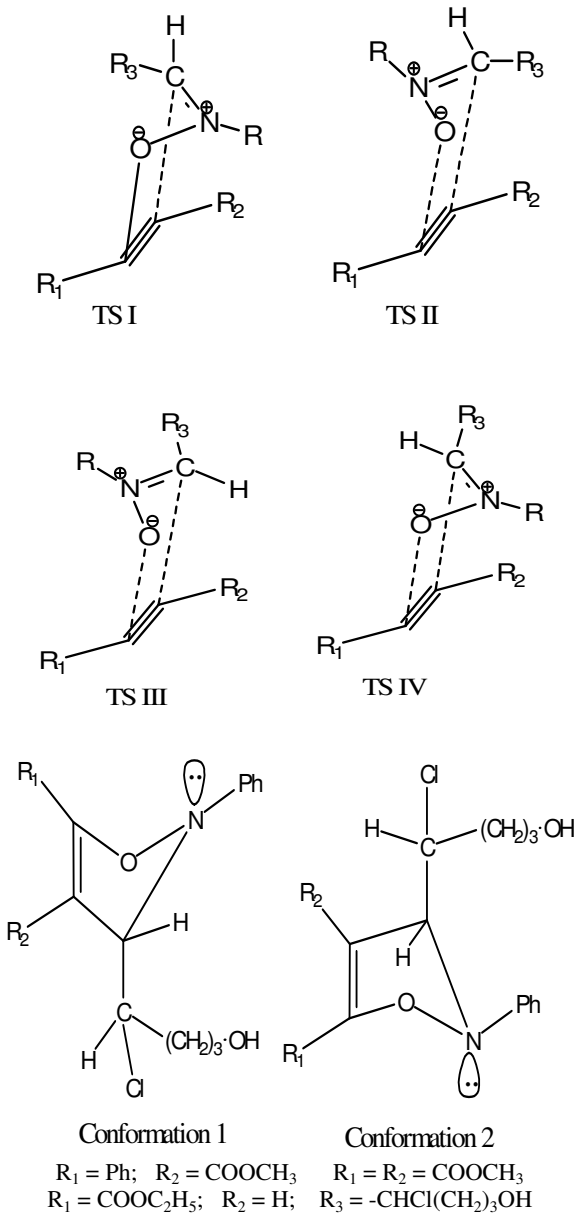


Figure 1

reaction conditions (RT), much faster reactions and high yield of products.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX1 881 machine as film for all the products. Mass spectra were recorded with a Jeol SX-102 (FAB) instrument. Elemental analyses (C,H,N) were perfomed with a Perkin-Elmer 2400 series CHN analyzer. TLC was carried out on Fluka silica gel TLC cards. N-phenylhydroxyl amine was prepared according to the published procedures[1,2]. All other reagents and solvents were used as received from commercial suppliers.

General procedure for the preparation of nitrone

N-phenyl-α-chloro nitrone was prepared following the same methodology as already reported for N-cyclohexyl-α-chloro nitrone[13,14]. N-Phenyl-hydroxylamine[1,2] (2.20 mmole) was added to chlorohydrin (1 equivalent) in dry ether (100 mL) and anhydrous $MgSO_4$. The reaction mixture was kept at RT with constant stirring with a magnetic stirrer under N_2 atmosphere for 8 hr. The formation of nitrone was monitored by TLC having R_f = 0.36. The nitrone was isolated under reduced pressure as white neddle shape crystals (m.p: 58°C, 93%, **Scheme I).**

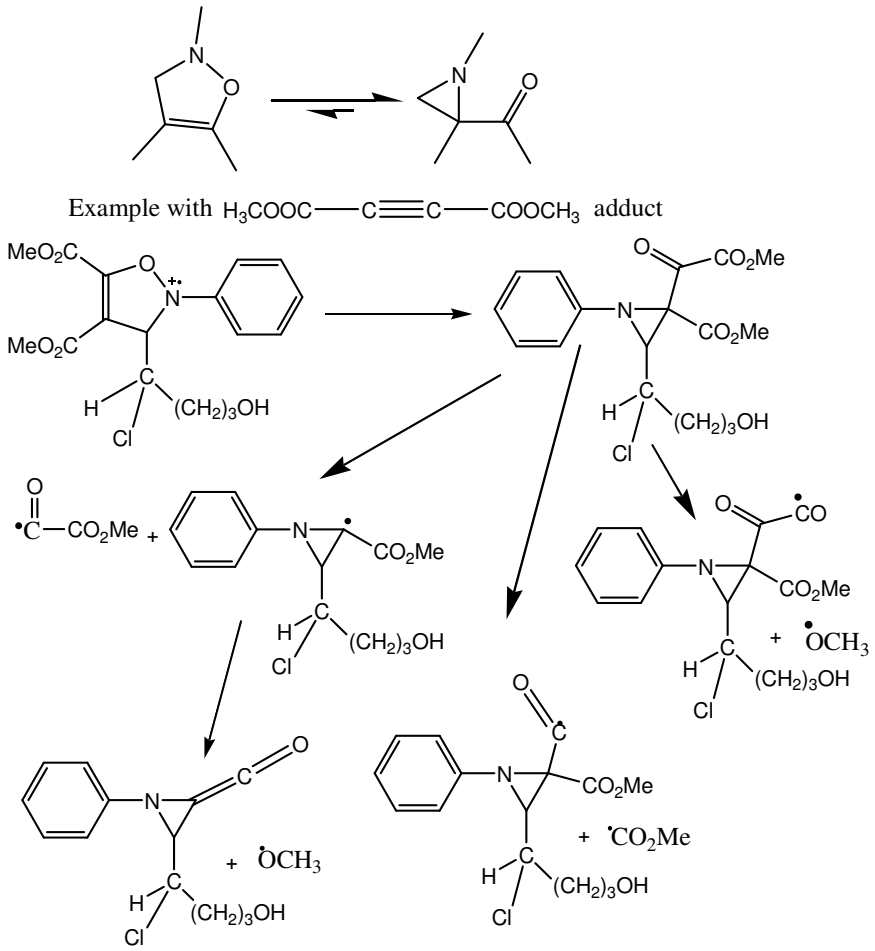
Nitrone 1. IR ($CHCl_3$): 3640-3440 (br), 1660(s), 1600(s), 1360(m), 1310(m), 770(s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.22 (d, 1H, CH=N$^+$), 7.10-6.95 (m, 5H, C_6H_5), 5.10-5.02 (br,1H, -OH, exchanged in D_2O), 4.30-4.15 (dd, 1H, *J*=6.16, 6.08 Hz, CHCl), 2.20-1.66 (m, 6H, CH_2 protons); ^{13}C NMR($CDCl_3$)**:** δ 142.6 (CH=N$^+$), 136-126 (6 signals, 6 aromatic carbons), 54 (CHCl), 43, 40, 37 (3 CH_2 carbons); HRMS-EI: Calcd. for $C_{11}H_{14}O_2NCl$, (M), 227.8173, Found; M$^+$, 227.8158.

General procedure for cycloaddition at elevated temperature

Initially the cycloaddition reaction was performed at elevated temperature in case of ethyl propiolate following the methodology of cyclo-addition reactions as already reported[13]. Nitrone **1** (2.20 mmoles) and ethyl propiolate (1 equivalent) was added in CH_2Cl_2 (20 mL) under N_2 atmosphere and the reaction mixture was refluxed for 12 hr. The reaction was monitored by TLC (R_f = 0.38, 0.33). The solvent was evaporated off and the products were isolated by column chromatography using ethyl acetate and hexane. But this methodology was not followed due to poor yield (34%) and decomposition of nitrone at elevated temperature.

General procedure for cycloaddition at room temperature

In a 100 mL conical flask, nitrone **1** (2.20 mmoles), ethyl propiolate (1 equivalent) was added to 50 mL dry ether and stirred at RT with a magnetic stirrer



Scheme III

under N_2 atmosphere for 12 hr. The progress of the reaction was monitored by TLC (R_f = 0.46, 0.40). After completion of the reaction, the solvent was evaporated under reduced pressure and the mixture of diastereoisomers were purified and separated by column chromatography using ethyl acetate-hexane to furnish white viscous liquids. **4a:** 73 mg, 70%; **4b:** 36 mg, 22 % **(Scheme II)**. This procedure was followed for other substrates listed in **Table I**.

(3S)-Methyl-3-(1-chloro-4-hydroxybutyl)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate, 2a

IR ($CHCl_3$): 3590-3460(br), 2920(s), 1760(s), 1665(m), 1430(m), 1360(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.55-7.38 (m, 10H, C_6H_5 hydrogens), 5.10-4.95 (br, 1H,-OH, exchangeable in D_2O), 4.55-4.40 (dd, 1H, *J*=9.22, 6.18 Hz, CHCl), 4.05-3.90 (d, 1H, *J*=9.2 Hz, C_3H), 3.60 (s, 3H,-$COOCH_3$), 1.95-1.72 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 168 (carbonyl carbon), 137-126 (6×2 aromatic carbons), 92 (CHCl), 88 (C_5), 73(C_3), 58 (C_4), 45(-$COOCH_3$), 36, 34, 33 (3 CH_2 carbons); MS: *m/z* 388 (M^+), 357, 329, 311, 283, 280, 203, 105, 77; HRMS-EI: Calcd. for $C_{21}H_{22}O_4NCl$ (M), 387.7000, Found: M^+, 387.6990.

(3R)-Methyl-3-(1-chloro-4-hydroxybutyl)-2,5-diphenyl-2,3-dihydroisoxazole-4-carboxylate, 2b

IR ($CHCl_3$): 3520-3440 (br), 2925(s), 1755(s), 1675(m), 1440(m), 1345(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52-7.35 (m, 10H, C_6H_5 hydrogens), 5.15-5.05 (br, 1H,-OH, exchangeable in D_2O), 4.54-4.43 (dd, 1H, *J*=2.52, 4.18 Hz, CHCl), 4.08-3.92 (d, 1H, *J*=2.54 Hz, C_3H), 3.62 (s, 3H,-$COOCH_3$), 1.95-1.50 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 168 (carbonyl carbon), 138-126 (6x2 aromatic carbons), 90 (CHCl), 87 (C_5), 76(C_3), 54 (C_4), 45 (-$COOCH_3$), 39, 35, 33 (3 CH_2 carbons); MS: *m/z* 388 (M^+), 357, 329, 311, 283, 280, 203, 105, 77; HRMS-EI: Calcd.

for $C_{21}H_{22}O_4NCl$ (M), 387.7000, Found: M^+, 387.6982.

(3S)-Dimethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate, 3a

IR ($CHCl_3$): 3545-3480 (br), 2820 (s),1745 (s),1700 (m),1670 (m),1420 (s),1260 (m),775 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75-7.54 (m, 5H, C_6H_5 protons), 5.22-5.05 (br, 1H, OH, exchanged in D_2O), 4.86-4.75 (d, 1H, *J*=9.25 Hz, C_3H), 4.26-4.10 (dd, *J*=6, 9.26 Hz, CHCl), 3.68 (s,3H,- $COOCH_3$), 3.56 (s,3H,-$COOCH_3$)-phe, 2.20-2.05 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169, 168.4 (carbonyl carbons), 133-126 (6 aromatic carbons), 94 (CHCl), 87.5 (C_5), 76 (C_3), 59.4 (C_4), 44, 43 (OCH_3), 36, 34, 30 (3 CH_2 carbons); MS: *m/z* 370 (M^+), 311, 293, 262, 234, 204, 108, 77, 59, 31; HRMS-EI: Calcd. for $C_{17}H_{20}O_6NCl$, (M), 369.5840, Found; M^+, 369.5828.

(3R)-Dimethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate, 3b

IR ($CHCl_3$): 3555-3485 (br), 2825 (s),1740 (s), 1710 (m), 1660 (m), 1425 (s), 1260(m), 770 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70-7.56 (m, 5H, C_6H_5 protons), 5.20-5.08 (br 1H, OH, exchanged in D_2O), 4.88-4.74 (d, 1H, *J*=2.58 Hz, C_3H), 4.36-4.26 (dd, *J*=4, 2.26 Hz, CHCl), 3.66 (s,3H,-$COOCH_3$), 3.54 (s,3H,-$COOCH_3$), 2.12-1.95 (m, 6H, CH_2 protons); ^{13}C NMR ($CDCl_3$): δ 169, 168 (carbonyl carbons), 134-126 (6 aromatic carbons), 95 (CHCl), 88.5 (C_5), 74 (C_3), 56 (C_4), 44, 42 (OCH_3), 36, 35, 30 (3 CH_2 carbons); MS: *m/z* 370 (M^+), 311, 293, 262, 234, 204, 108, 77, 59, 31; HRMS-EI: Calcd. for $C_{17}H_{20}O_6NCl$, (M), 369.5840, Found; M^+, 369.5822.

(3S)-Ethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate, 4a

IR($CHCl_3$): 3560-3490(br), 2945(s), 1770(m), 1680(s), 1430(m), 1260(m), 780(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02-6.92 (m, 5H, C_6H_5), 5.10-5.02 (br, 1H, OH, exchanged in D_2O), 4.80-4.64 (t, 1H, *J*=9.26 Hz, C_3H), 4.26-4.12 (dd, 2H, *J*=6.24, 6.36 Hz, $COOCH_2CH_3$), 3.82-3.50 (dd, 1H, *J*=6, 9.28 Hz, CHCl), 3.35-3.26 (d, 1H, *J*=7.5 Hz, C_4H), 3.00-2.62 (m, 6H, CH_2 protons), 1.40-1.24 (t, 3H, *J*=4.36 Hz, $COOCH_2CH_3$); ^{13}C NMR($CDCl_3$): δ 168.4 (carbonyl carbon), 133-126 (6 aromatic carbons), 93 (CHCl), 86 (C_5), 78 (C_3), 55 (C_4), 32, 30 ($COOCH_2CH_3$), 26, 25, 23 (3 CH_2 carbons); MS: *m/z* 326 (M^+), 295, 253, 249, 219, 108, 77, 73; HRMS-EI: Calcd. for $C_{16}H_{20}O_4NCl$ (M), 325.5944, Found; M^+, 325.5932.

(3R)-Ethyl-3-(1-chloro-4-hydroxybutyl)-2-phenyl-2,3-dihydroisoxazole-5-carboxylate, 4b

IR($CHCl_3$):3550-3480(br), 2955(s), 1760(m), 1680(s), 1440(m), 1265(m), 770(s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.04-6.94 (m, 5H, C_6H_5), 5.14-5.02 (br, 1H, OH, exchanged in D_2O), 4.83-4.62 (t, 1H, *J*=2.26 Hz, C_3H), 4.22-4.10 (dd, 2H, *J*=2.24, 4.06 Hz, $COOCH_2CH_3$), 3.80-3.52 (dd, 1H, *J*=4, 2.28 Hz, CHCl), 3.38-3.22 (d, 1H, *J*=4.12 Hz, C_4H), 3.10-2.64 (m, 6H, CH_2 protons), 1.46-1.20 (t, 3H, *J*=5.24 Hz, $COOCH_2CH_3$); ^{13}C NMR($CDCl_3$): δ 168 (carbonyl carbon), 134-127(6 aromatic carbons), 95 (CHCl), 86.5 (C_5), 76 (C_3), 55.5 (C_4), 31, 30 ($COOCH_2CH_3$), 28, 26, 24 (3 CH_2 carbons); MS: *m/z* 326 (M^+), 295, 253, 249, 219, 108, 77, 73; HRMS-EI: Calcd. for $C_{16}H_{20}O_4NCl$ (M), 325.5944, Found; M^+, 325.5930.

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